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Review

Golgi structure in stress sensing and apoptosis

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Abstract

The Golgi complex in mammalian cells is composed of polarized stacks of flattened cisternal membranes. Stacks are connected by tubules forming a reticular network of membranes closely associated with the microtubule-organizing center. While the Golgi structure is important for the efficient processing of secretory cargo, the organization of the mammalian Golgi complex may indicate potential functions in addition to the processing and sorting of cargo. Similar to the endoplasmic reticulum stress response pathway, the Golgi complex may initiate signaling pathways to alleviate stress, and if irreparable, trigger apoptosis. Here, we review recent experimental evidence suggesting that the elaborate structure of the Golgi complex in mammalian cells may have evolved to sense and transduce stress signals.

Keywords: Golgi complex; Golgin; Caspase cleavage; Apoptosis; Golgi structure; Signaling

1. Introduction

The Golgi complex is essential for the processing and sorting of lipids and proteins en route from the endoplasmic reticulum (ER) to the plasma membrane and other destinations [1]. Since the discovery of the Golgi complex over 100 years ago, researchers have been fascinated with its elaborate morphology. While certain structural features of the Golgi complex are conserved between species, other structural aspects may have evolved to facilitate specialized functions, such as cell cycle control or locomotion. Although the role of Golgi structure in the proper and efficient transport of secretory cargo has been well documented, the role of the Golgi complex as a potential platform to both initiate and integrate cell-signaling events has gathered increasing support.

In most higher eukaryotic cells, the Golgi complex consists of multiple flattened cisternal membranes arranged in close apposition to each other to form stacks. Stacks are polarized, consisting of a *cis*-side associated with a tubular reticular network of membranes (*cis*-Golgi network, CGN), a medial area of disc-shaped flattened cisternae, and a *trans*-side associated with another tubular reticular membrane network (*trans*-Golgi network, TGN). In mammalian cells, individual Golgi stacks are further connected laterally with equivalent cisternae of different stacks by tubules, to create a ribbon structure that is localized in a juxta-nuclear region. In addition, ER tubules devoid of ribosomes are closely apposed to *trans*-Golgi cisternae of mammalian cells [2,3]. In the yeast *S. cerevisiae*, Golgi structure shows less overall organization, with individual cisternae dispersed throughout the cell. In insect cells, Golgi cisternae form stacks but the stacks are usually dispersed throughout the cytoplasm [4,5]. While the general conservation of Golgi function implies an essential role in the processing and transport of cargo, the more elaborate Golgi complex structure in mammalian cells hints at additional potential functions.

Originally, the Golgi complex was thought to be a static organelle, but it is actually a highly dynamic structure. The steady-state structure of Golgi stacks is partly a consequence of the balance of anterograde and retrograde transport through the Golgi. The inhibition of ER-to-Golgi traffic by either osmotic stress [6] or drugs [7] causes the Golgi to collapse into the ER due to unbalanced retrograde traffic. Temperature blocks that inhibit exit from either the *cis*-Golgi or *trans*-Golgi networks result in significant swelling

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caused by the accumulation of anterograde cargo in the CGN or TGN [8–10]. These observations underlie the dynamic nature of Golgi structure and support the idea that the maintenance of the steady-state structure of the Golgi complex requires an appropriate balance of inward and outward membrane traffic.

However, membrane traffic alone does not define Golgi structure. An increasing number of proteins, including cytoskeletal proteins, have been shown to localize to the Golgi and are required for proper Golgi structure. Recent studies have highlighted the importance of both the expression and post-translational modifications of these proteins to Golgi structure [11,12]. The sensitivity of Golgi structure to both the dynamic equilibrium of membrane traffic and the integrity of Golgi-associated structural proteins suggests that the cell closely coordinates both of these aspects to maintain the steady state structure of the Golgi complex. Golgi structural proteins may be uniquely poised to sense and potentially respond to changes in Golgi structure.

In this review, we discuss recent studies illustrating the importance of Golgi structural proteins in Golgi organization, and use the paradigm of stress-induced apoptotic signaling as an example of how these proteins may monitor and communicate Golgi structure to the rest of the cell.

2. Golgi structural components

The identification of a detergent-insoluble Golgi matrix [13,14] and an increasing number of Golgi-localized cytoskeleton binding proteins suggests that the structure of the mammalian Golgi complex may be organized by a cytoplasmic "exoskeleton" [12]. This exoskeleton is proposed to be an extensive meshwork of cytoskeletal and Golgi proteins that sequester and align resident enzymes, limit diffusion, organize membrane domains, and provide shape to the Golgi complex. Additionally, a number of signaling proteins are localized to Golgi membranes and may be positioned to sense and convey changes in Golgi structure [15–17].

During apoptosis, the Golgi complex is dramatically disassembled due to changes in the Golgi exoskeleton and other Golgi structural proteins. Traditionally, apoptotic Golgi disassembly has been viewed as a late event allowing for Golgi disposal. Below, we speculate that changes in Golgi structure may also trigger and propagate specific stress signals resulting in adaptation or, if the stress is too severe, apoptosis.

2.1. Microtubules

The intimate association of the Golgi complex with the cytoskeleton was first suggested by the observation that in mammalian cells, the Golgi complex colocalizes with the microtubule organizing center (MTOC). Microtubules were later shown to play an active role in the positioning of the Golgi complex by use of microtubule disruptive drugs [18,19]. Microtubule disassembly causes the dispersal of the Golgi complex into fragments, termed ministacks, throughout the cell. Surprisingly, it was shown that after a short period of adaptation these ministacks were able to properly glycosylate and transport constitutive secretory cargo [20,21]. This observation, in conjunction with the lack of microtubule dependent localization of *S. cerevisiae* Golgi cisternae or Golgi stacks in insect cells, suggests that the juxta-nuclear positioning of the Golgi complex is not essential for the processing and transport of secretory cargo in mammalian cells. Therefore, the centralized localization of the Golgi complex in mammalian cells suggests a possible specialized function independent of membrane traffic.

In fibroblasts, the minus-ends of microtubules are organized in asters closely associated with the centrosome. Golgi elements from ER exit sites are transported along microtubule tracks by dynactin/dynein complexes towards the minus-ends of microtubules [22,23]. Once localized in a juxta-nuclear position, the Golgi complex is anchored in position by a number of microtubule-binding proteins located on the cytoplasmic face of *cis*-Golgi membranes [24,25]. The Golgi/centrosome localization of proteins like AKAP450 [26] and myomegalin [27], which have the capacity to bind several molecules involved in cAMP- and Rho/Rac/Cdc42-dependent signaling, suggests that the juxta-nuclear position and structure of the Golgi complex may help regulate and coordinate the remodeling of cellular architecture during events such as polarization, mitosis, and apoptosis.

2.2. Microfilaments, spectrin, and associated proteins

Actin microfilaments were first shown to be involved in Golgi morphology and subcellular localization by the use of microfilament disrupting drugs. The disruption of microfilaments causes the Golgi complex to collapse even further into the centrosomal region [28,29]. Additional analysis showed that the Golgi cisternae persist in stacks, which remain linked to microtubules. Golgi localization of a number of actin-binding proteins, including tropomyosin [30], centractin [31] and spectrin [32], further supports an active role for actin in Golgi structure.

Several isoforms of β-spectrin, as well as key membrane anchoring proteins, have been isolated from Golgi membranes [32–34]. Spectrin is a cytoskeletal protein that controls membrane organization, stability and shape, and links membranes to the major filament systems and associated motors. Spectrin is proposed to simultaneously bind to integral Golgi membrane proteins, cytosolic proteins and specific phospholipids creating a two-dimensional lattice of filaments on the cytoplasmic face of Golgi membranes [12]. By doing so, spectrin can organize

multifunctional scaffolds at the membrane interface, integrating signaling molecules, structural proteins, and lipids. The disruption of Golgi spectrin by the expression of dominant negative constructs blocks membrane traffic and, in some cells, results in collapse of the Golgi ribbon into a compact juxta-nuclear structure [35].

The recruitment of spectrin to Golgi membranes is primarily regulated by PtdIns(4,5)P2 in an ADP-ribosylation factor-dependent manner [36]. The biophysical properties of the spectrin lattice can be further modulated by post-translational modifications, such as phosphorylation. Siddhanta et al. showed that when PtdIns(4,5)P2 levels are diminished, βIII spectrin is phosphorylated and released from Golgi membranes resulting in Golgi fragmentation [37]. Ongoing research attempts to answer how the dynamic nature of Golgi membranes is maintained in the presence of the spectrin exoskeleton and how this relates to the less organized structure and function of the Golgi in the yeast *S. cerevisiae*, which does not have spectrin.

2.3. Golgins and GRASPs

Golgins and Golgi reassembly and stacking proteins (GRASPs) have been implicated as components of the Golgi exoskeleton [38,39]. Members of the golgin family were first identified as autoantigens in a variety of autoimmune diseases, but the definition has been expanded to include any Golgi-localized protein that contains an extensive coiled-coil domain. The golgin family is diverse and includes peripheral membrane proteins such as GM130 [14], golgin-97 [40], golgin-160 [41,42], golgin-230/245 [43,44], and golgin-45 [47], as well as the integral membrane proteins golgin-67 [45], golgin-84 [46], and giantin [48]. While all identified yeast golgins have human orthologs, the human golgin family includes a number of additional members [49]. The increased number of human golgins may reflect additional structural and functional demands not present in yeast.

It is unclear whether or not golgins represent a functional family. Some studies have implicated certain golgins in vesicle tethering and Golgi structure. GM130 and giantin have been most extensively studied. Giantin on transport vesicles is thought to interact via p115 with GM130 bound to *cis*-Golgi membranes in a Rab1-dependent manner [50]. This interaction is thought to increase the specificity and/or efficiency of the SNARE (soluble NSF-attachment proteins receptor)-mediated recognition and fusion of transport vesicles [51]. While it is unclear if the proposed mechanism of vesicle tethering attributed to GM130 and giantin can be generalized to other family members, a number of golgins have been implicated in a variety of membrane transport pathways and in Golgi structure.

Using a cell-free assay for mitotic disassembly and reassembly of the Golgi, GRASP65 was identified as an *N*-ethylmaleimide-sensitive protein important for Golgi membrane stacking [52]. GRASP65 is proposed to regulate docking interactions between Golgi cisternae, leading to cisternal stacking through interactions with GM130. GM130 and GRASP65 are both phosphorylated in mitosis, contributing to regulated Golgi disassembly [53,54]. The microinjection of antibodies or the overexpression of the C-terminal fragment of GRASP65 prevents mitotic Golgi disassembly and blocks entry into mitosis [55]. However, fragmentation of the Golgi complex by drugs prior to these treatments relieves this mitotic block. Preisinger et al. showed that phosphorylated GRASP65 acts as a docking site for polo-like kinase 1 (Plk1) [56]. Plk1 likely phosphorylates substrates important for regulating Golgi structure and passage through mitosis. These observations suggest that the dispersion of juxta-nuclear Golgi stacks links Golgi structure and cell cycle control.

Recently a medial-Golgi complex containing GRASP55 [57] and golgin-45 [47] was identified. The depletion of golgin-45 by RNA interference results in Golgi disassembly and inhibition of secretory protein transport [47]. A number of other golgins have been implicated in the maintenance of Golgi structure. The depletion of golgin-97 by RNA interference results in Golgi fragmentation and inhibition of endosome-to-TGN retrograde traffic of cholera toxin B fragment [58]. Similarly, the depletion of golgin-84 leads to Golgi fragmentation, which results in a partial inhibition of cell surface delivery of the vesicular stomatitis virus G protein [59]. Taken together, these results suggest that golgins and the proteins with which they interact are necessary for Golgi structure and a variety of membrane trafficking pathways. Post-translational modifications of specific golgins and GRASPs may allow for the precise regulation of Golgi structure and trafficking pathways.

3. Apoptosis and the Golgi complex

3.1. General apoptotic machinery

Apoptosis is an evolutionarily conserved programmed cell death pathway designed to remove extraneous or damaged cells without inducing inflammation [60,61]. During apoptosis, cells are disassembled and packaged into membrane-bound blebs bearing signals that stimulate surrounding cells to pihagocytose and eliminate them. Apoptosis is a highly regulated process that can be mediated by a diverse array of both intrinsic (e.g. DNA damage) and extrinsic (e.g. death receptor ligation) stress stimuli. The activation of apoptosis by either intrinsic or extrinsic stress converges into a common amplification pathway involving mitochondrial membrane permeabilization (MMP). MMP causes the release of factors that potentiate apoptotic progression.

Caspases are the central mediators of apoptotic cell death [62,63]. Caspases are cysteine proteases that cleave after

aspartate residues within specific proteins, irreversibly modifying target protein function. Caspases are synthesized as zymogens with low intrinsic activity but can be fully activated by cleavage, releasing an inhibitory prodomain and separating the protease subunits. Currently, 14 mammalian caspases have been identified, although not all have been implicated in apoptosis. Apoptotic caspases are generally divided into two classes, initiator caspases (including caspase-8, and -9) and effector caspases (including caspase-3 and -7) [64]. Initiator caspases have characteristically long prodomains, which mediate interactions with adaptor molecules. Adaptor recruitment of initiator caspases drives caspase oligomerization resulting in the initial activation of initiator caspases. Following oligomerization, initiator caspases undergo autocatalytic cleavage, which promotes stable oligomerization and further enhances the catalytic activity [65]. Initiator caspases can then proteolytically activate effector caspases, igniting a proteolytic cascade leading to the cleavage of a relatively small subset of cellular proteins. Target protein cleavage results in disassembly of organelles, cleavage of DNA, and packaging of cell contents into membrane bound blebs.

Triggering apoptotic cell death requires tipping the balance between pro- and antiapoptotic regulators. The Bcl-2 family of proteins plays a pivotal role in this decision by regulating both MMP and caspase activation [66,67]. The Bcl-2 family includes both pro- and anti-apoptotic members. Some anti-apoptotic members (e.g. Bcl-2 and Bcl-xL) act to preserve mitochondrial membrane integrity by sequestering mitochondrial proapoptotic factors. These anti-apoptotic members are antagonized by pro-apoptotic members (e.g., Bax and Bak) that promote the release of pro-apoptotic factors from the mitochondria by the induction of pores into the mitochondria outer membrane or by dysregulation of existing pores. While Bcl-2 proteins are thought to primarily act at the mitochondria, recent studies have suggested a role for Bcl-2 family members in the local activation of apoptosis at other organelles. The pro-apoptotic Bcl-2 family member, Bim, was shown to translocate to the endoplasmic reticulum (ER) during ER-stress [68]. The ER translocation and accumulation of Bim and/or other pro-apoptotic Bcl-2 members may overwhelm the anti-apoptotic effects of other Bcl-2 members, such as Bcl-xL, present on ER membranes, allowing for release of ER Ca^{2+} stores and/or local caspase activation resulting in apoptosis [69].

Apoptotic signaling can be further regulated by the inhibitor of apoptosis protein (IAP) family of proteins, which inhibit specific caspases. IAPs are defined by the presence of at least one baculovirus IAP repeat (BIR) domain. IAPs can bind directly to the active site of specific caspases inhibiting their catalytic activity [70,71]. Some IAPs may also function as E3 ligases, targeting caspases and other pro-apoptotic proteins for proteasomal degradation [72,73]. IAPs are therefore able to regulate apoptosis by the repression of caspase activation.

3.2. Apoptotic machinery at the Golgi complex

The clustering of both pro-apoptotic and anti-apoptotic machinery at subcellular sites distinct from mitochondria, such as the ER and Golgi, suggests that the cell may sense specific stress signals initiated at distinct localizations [61,74]. The discovery of a pool of caspase-2 localized to the cytoplasmic face of the Golgi complex indicates that caspase-2 may play a key role in apoptotic signaling at the Golgi complex [75]. Caspase- 2 is unique in that it possesses a long prodomain characteristic of initiator caspases but the substrate specificity of an effector caspase. Caspase-2 is classified as an initiator caspase by virtue of both its long prodomain and its activation by oligomerization followed by autocatalytic cleavage [76]. The Golgi localization of caspase-2 implies that it is positioned to interact with upstream apoptotic regulators at the Golgi, resulting in the cleavage of substrates enriched at the Golgi, such as golgin-160 [75] and giantin [77]. Mancini et al. [75] showed that golgin-160 can be cleaved by caspases-2, -3, and -7. However, the cleavage of golgin-160 by caspase-2 occurs rapidly and precedes caspase-3 cleavage, indicating an early role for caspase-2 activation at the Golgi [75]. While the activation of Golgi caspase-2 can occur rapidly, the mechanism of activation is unknown.

An IAP called Apollon or BRUCE (BIR repeat containing ubiquitin-conjugating enzyme) is localized in the Golgi region [78] and may act as a negative regulator of caspase-2 activation at the Golgi. *Drosophila* BRUCE suppresses cell death induced by pro-apoptotic proteins Reaper and Grim [79]. Recent studies have confirmed the anti-apoptotic role of BRUCE in mammalian cells [80,81]. This leads to the possibility that BRUCE may prevent caspase activation at the Golgi complex.

Death receptors, including tumor necrosis factor receptor-1 and Fas, are predominantly localized during steady state at the Golgi complex [82–84]. Since the ligands for these receptors are extracellular, some membrane trafficking must occur for maximal signaling. Hippi (Hip-1 protein interactor) is also at least partially localized to the Golgi complex [85]. Hip-1 interacts strongly with wild-type huntingtin, but less well with glutamine-expanded mutant forms of huntingtin, which are implicated in Huntington disease. Released Hip-1 is postulated to interact with Hippi to activate caspsase-8, which leads to apoptotic death of neurons [85]. It is not yet clear whether Hip-1 and Hippi play a role in regulating apoptosis through capsase-8 in other cell types. It is likely that more apoptotic regulatory components will be identified and localized to the Golgi complex, supporting the importance of the Golgi in the integration of stress signaling.

3.3. Apoptotic Golgi disassembly

During apoptosis, secretory traffic is blocked, and the Golgi complex undergoes disassembly, which is morpho-

logically similar to mitotic disassembly [77,86]. The interconnected ribbon structure of the Golgi complex is lost, and Golgi stacks no longer closely associate with the MTOC. Individual cisternae are further disassembled into clusters of vesicles and tubules dispersed throughout the cell. A growing number of proteins implicated in Golgi structure and membrane trafficking are cleaved by caspases during apoptosis. These proteins include golgin-160 [75], GRASP65 [87], giantin [77], and GM130 [88–90] as well as the vesicle transport protein p115 [88], the t-SNARE syntaxin-5 [77], the intermediate chain of dynein, and the $p150^{Glued}$ subunit of dynactin [91].

Caspase cleavage of at least a subset of these proteins is required for efficient apoptotic disassembly of the Golgi. The expression of caspase-resistant mutants of golgin-160 [75,92], GRASP65 [87], or p115 [88] delays apoptotic Golgi disassembly. The caspase cleavage of Golgi structural proteins may play a role similar to that of mitotic phosphorylation in promoting Golgi disassembly. While not all targets of mitotic phosphorylation are likely to be caspase substrates, GRASP65 is both reversibly phosphorylated during mitosis [53] and irreversibly cleaved during apoptosis [87] leading to Golgi disassembly. This supports the idea that reversible mitotic disassembly and irreversible apoptotic disassembly may follow similar pathways.

3.4. Apoptotic signaling from the Golgi complex?

After some apoptotic stimuli, caspase cleavage of Golgi structural proteins is likely to be the downstream result of effector caspase activation, allowing the packaging of Golgi remnants into apoptotic blebs for disposal. On the other hand, recent studies have implicated cleavage of Golgi proteins in upstream apoptotic signaling events. Cells expressing non-cleavable golgin-160 demonstrate a delayed response to apoptotic stimuli that cause ER stress (e.g. thapsigargin and dithiothreitol) or ligate death receptors (e.g. tumor necrosis factor receptor-1 and Fas) [92]. This is not a result of the inability to disperse Golgi stacks, since apoptosis was still delayed in these cells when Golgi structure was disrupted with drugs prior to initiating apoptosis. Importantly, delayed apoptotic response was not observed with all pro-apoptotic stimuli. These cells respond normally to a DNA-damaging agent, a protein synthesis inhibitor, and a broad-spectrum kinase inhibitor. Therefore, the cleavage of golgin-160 at the Golgi appears to be required for the progression of apoptosis induced by specific stimuli. Maag et al. showed that the expression of non-cleavable golgin-160 also prevents the drug-specific cleavage of endogenous golgin-160 due to a block in upstream caspase activation [92]. The mechanism by which caspase-resistant golgin-160 inhibits the activation of initiator caspases and progression of apoptosis is currently being addressed.

Interestingly, the internal golgin-160 fragment corresponding to that generated by caspase-2 is targeted to the nucleus when exogenously expressed [93]. Thus, if this caspase-2 cleavage fragment is released from Golgi membranes during Golgi stress, it is likely to be translocated to the nucleus. It is possible that this fragment could influence the stress response by regulating gene expression to either alleviate stress, or if irreparable, promote apoptosis. The carboxy-terminal caspase fragment of the Golgi vesicle transport protein p115 accumulates in the nucleus when overexpressed, and is able to promote both Golgi fragmentation and apoptosis [88]. p115 is cleaved by the effector caspase-3, which suggests that unlike golgin-160, the cleavage of p115 most likely is a late event when the cell is already committed to die. Chiu et al. were able to demonstrate that the induction of apoptosis by the C-terminal fragment p115 was independent of Golgi disassembly [88], supporting the idea that the caspase-cleavage fragments of some Golgi structural proteins may actively regulate apoptosis.

4. Stress sensing and Golgi structure: paradigms and speculations

Experimental evidence suggests that several organelles are capable of sensing and relaying pro-apoptotic signals, culminating in the proteolytic activation of caspases and cell death [61]. Each organelle is likely to be uniquely poised and equipped to sense specific stimuli related to their function and structure. For example, the ER is a major site for folding, modification and assembly of newly synthesized transmembrane and secretory proteins. The ER has evolved a stress response pathway, the unfolded protein response (UPR), to cope with the accumulation of unfolded or misfolded proteins [94]. ER stresses known to induce the UPR include the inhibition of protein glycosylation, reduction of disulfide bonds, and depletion of ER lumenal Ca^{2+}. ER resident chaperones and Ca^{2+}-binding proteins monitor and evaluate these processes. The activation of the UPR has been shown to induce the expression of chaperones, attenuate translation, and degrade misfolded proteins in an attempt to alleviate the stress. Prolonged ER stress resulting in irreparable damage leads to apoptosis. The local activation of caspases at ER membranes and potentiation of MMP by release of ER Ca^{2+} are involved. Due to its central function in protein folding, the ER has evolved a unique ability to monitor the folding state of proteins and respond to improperly folded proteins by first adapting or, if the damage is too severe, causing cell death.

Evidence suggests that there is a post-ER quality control system that operates at the Golgi complex to eliminate mutant or misfolded proteins that escape the ER [95,96]. It is also likely that the Golgi complex can sense and transduce unique stress signals. Similar to ER stress signaling, the Golgi complex may initiate stress signaling through a complement of Golgi-localized machinery. Apoptosis would

result if the stress cannot be alleviated. Deciphering the precise role of the Golgi complex in stress signaling will require the identification of signals that originate at the Golgi complex. Although there are currently no well-documented Golgi-specific stresses, potential inducers of Golgi stress include the disruption of post-ER protein modifications or folding, membrane traffic overload, changes in Golgi pH or ion content, and viral assembly and budding at Golgi membranes.

It is tempting to speculate that the elaborate structure of the Golgi complex in mammalian cells may have evolved to sense and transduce specific stress signals. As has been proposed for mitotic progression [55], the dispersion of the juxtanuclear Golgi ribbon during cell stress might be monitored. Perturbations of cytoskeletal elements could certainly impact Golgi structure and positioning. Changes in Golgi position could also disrupt ER-*trans* Golgi connections, which may be involved in ceramide trafficking and sphingomyelin synthesis [3,97,98]. If sphingomyelin synthesis is disrupted, the accumulation of ceramide could stimulate signaling directly or indirectly by causing changes in membrane properties [99]. Could these structural changes trigger progression of stress signaling?

Another interesting possibility is that stress signals could lead to lipid scrambling of Golgi membrane bilayers, similar to phosphatidylserine exposure at the plasma membrane during apoptosis [100]. The glycolipid GD3, which is normally synthesized on the lumenal face of Golgi membranes, is translocated to mitochondria during apoptosis, where it is postulated to promote MMP [101,102]. This suggests that GD3 traffics from the lumenal leaflet of Golgi or endosome membranes to the mitochondria, but the mechanism is not understood. Interestingly, if active GD3 synthase is retained in the ER, GD3 is not transported to mitochondria after apoptotic stimuli, and apoptosis is inhibited [103]. This result implies that Golgi localization of GD3 may be critical for its transport to mitochondria. One possibility is that stress-induced lipid scrambling of Golgi membranes could make GD3 available to be trafficked to mitochondria. Another Golgi lipid, semilysobisphosphatidic acid, is also found in mitochondria following stimulation with Fas ligand [104,105], which supports the importance of lipid trafficking from the Golgi to the mitochondria during apoptosis.

Changes in Golgi cisternal structure, including unstacking or swelling, could also transduce a stress signal. For example, changes in membrane curvature induced by swelling could result in the recruitment or release of specific proteins allowing for the regulation of signaling complexes. Changes in the thickness of Golgi membranes (e.g. due to differences in cholesterol or sphingolipid content) might also be sensed by a subset of transmembrane proteins with hydrophobic domains of defined lengths. It will be important to carefully assess changes in Golgi structure once specific stresses leading to apoptosis are identified.

5. Future perspectives

Golgi-localized caspase-2 may be the best key to unlocking the role of the Golgi complex in apoptotic signaling. Determining which stimuli activate Golgi-localized caspase-2 will help identify stress signals that originate at the Golgi complex. Understanding the mechanism by which these stresses are sensed at the Golgi complex and activate caspase-2 may shed some light on the role of Golgi structure in stress signaling. In addition, it will be important to determine whether or not the Golgi complex initiates a stress repair response analogous to the UPR prior to initiating apoptosis. Once Golgi-specific stimuli are identified, it will be interesting to determine the gene expression profile of Golgi and other secretory pathway proteins during apoptosis. In assessing the role of Golgi structure in stress signaling, it will be important to determine the precise structural changes that occur after a stress signal. Does the disassembly pathway of the Golgi during apoptosis differ following different stress signals? What is the contribution of cleavage or modification of golgins and other Golgi structural proteins? Determining the consequence of release from the Golgi of proteins or protein fragments, like the N-terminal fragments of golgin-160, will help determine if these proteins have an active role in stress signaling. Golgi lipids have been implicated in promoting apoptosis, but how are these lipids trafficked to and from the Golgi during apoptosis? Many questions remain regarding stress signaling at the Golgi complex. Answers to these questions will help evaluate the hypothesis that the elaborate structure of Golgi complex in mammalian cells has evolved to sense and transduce specific stress signals.

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References

[1] M.G. Farquhar, G.E. Palade, The Golgi apparatus: 100 years of progress and controversy, Trends Cell Biol. 8 (1998) 2–10.
[2] A.R. Hand, C. Oliver, Relationship between the Golgi apparatus, GERL, and secretory granules in acinar cells of the rat exorbital lacrimal gland, J. Cell Biol. 74 (1977) 399–413.
[3] M.S. Ladinsky, D.N. Mastronarde, J.R. McIntosh, K.E. Howell, L.A. Staehelin, Golgi structure in three dimensions: functional insights from the normal rat kidney cell, J. Cell Biol. 144 (1999) 1135–1149.
[4] H. Stanley, J. Botas, V. Malhotra, The mechanism of Golgi segregation during mitosis is cell type-specific, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 14467–14470.
[5] C. Rabouille, D.A. Kuntz, A. Lockyer, R. Watson, T. Signorelli, D.R. Rose, M. van den Heuvel, D.B. Roberts, The *Drosophila* GMII gene encodes a Golgi alpha-mannosidase II, J. Cell. Sci. 112 (Pt 19) (1999) 3319–3330.

[6] T.H. Lee, A.D. Linstedt, Osmotically induced cell volume changes alter anterograde and retrograde transport, Golgi structure, and COPI dissociation, Mol. Biol. Cell 10 (1999) 1445–1462.
[7] A. Dinter, E.G. Berger, Golgi-disturbing agents, Histochem. Cell Biol. 109 (1998) 571–590.
[8] G. Griffiths, S. Pfeiffer, K. Simons, K. Matlin, Exit of newly synthesized membrane proteins from the trans cisterna of the Golgi complex to the plasma membrane, J. Cell Biol. 101 (1985) 949–964.
[9] K.S. Matlin, K. Simons, Reduced temperature prevents transfer of a membrane glycoprotein to the cell surface but does not prevent terminal glycosylation, Cell 34 (1983) 233–243.
[10] M.S. Ladinsky, C.C. Wu, S. McIntosh, J.R. McIntosh, K.E. Howell, Structure of the Golgi and distribution of reporter molecules at 20 degrees C reveals the complexity of the exit compartments, Mol. Biol. Cell 13 (2002) 2810–2825.
[11] F.A. Barr, B. Short, Golgins in the structure and dynamics of the Golgi apparatus, Curr. Opin. Cell Biol. 15 (2003) 405–413.
[12] M.A. De Matteis, J.S. Morrow, Spectrin tethers and mesh in the biosynthetic pathway, J. Cell. Sci. 113 (Pt 13) (2000) 2331–2343.
[13] P. Slusarewicz, T. Nilsson, N. Hui, R. Watson, G. Warren, Isolation of a matrix that binds medial Golgi enzymes, J. Cell Biol. 124 (1994) 405–413.
[14] N. Nakamura, C. Rabouille, R. Watson, T. Nilsson, N. Hui, P. Slusarewicz, T.E. Kreis, G. Warren, Characterization of a *cis*-Golgi matrix protein, GM130, J. Cell Biol. 131 (1995) 1715–1726.
[15] Z. Freyberg, A. Siddhanta, D. Shields, "Slip, sliding away": phospholipase D and the Golgi apparatus, Trends Cell Biol. 13 (2003) 540–546.
[16] C. Preisinger, F.A. Barr, Signaling pathways regulating Golgi structure and function, Sci. STKE 2001 (2001) PE38.
[17] V.K. Chiu, T. Bivona, A. Hach, J.B. Sajous, J. Silletti, H. Wiener, R.L. Johnson II, A.D. Cox, M.R. Philips, Ras signalling on the endoplasmic reticulum and the Golgi, Nat. Cell Biol. 4 (2002) 343–350.
[18] A.A. Rogalski, S.J. Singer, Associations of elements of the Golgi apparatus with microtubules, J. Cell Biol. 99 (1984) 1092–1100.
[19] J. Thyberg, S. Moskalewski, Microtubules and the organization of the Golgi complex, Exp. Cell Res. 159 (1985) 1–16.
[20] N.B. Cole, N. Sciaky, A. Marotta, J. Song, J. Lippincott-Schwartz, Golgi dispersal during microtubule disruption: regeneration of Golgi stacks at peripheral endoplasmic reticulum exit sites, Mol. Biol. Cell 7 (1996) 631–650.
[21] A.A. Rogalski, J.E. Bergmann, S.J. Singer, Effect of microtubule assembly status on the intracellular processing and surface expression of an integral protein of the plasma membrane, J. Cell Biol. 99 (1984) 1101–1109.
[22] I. Corthesy-Theulaz, A. Pauloin, S.R. Pfeffer, Cytoplasmic dynein participates in the centrosomal localization of the Golgi complex, J. Cell Biol. 118 (1992) 1333–1345.
[23] J.K. Burkhardt, C.J. Echeverri, T. Nilsson, R.B. Vallee, Overexpression of the dynamitin (p50) subunit of the dynactin complex disrupts dynein-dependent maintenance of membrane organelle distribution, J. Cell Biol. 139 (1997) 469–484.
[24] R.M. Rios, M. Bornens, The Golgi apparatus at the cell centre, Curr. Opin. Cell Biol. 15 (2003) 60–66.
[25] A.D. Linstedt, Positioning the Golgi apparatus, Cell 118 (2004) 271–272.
[26] M. Takahashi, H. Shibata, M. Shimakawa, M. Miyamoto, H. Mukai, Y. Ono, Characterization of a novel giant scaffolding protein, CG-NAP, that anchors multiple signaling enzymes to centrosome and the golgi apparatus, J. Biol. Chem. 274 (1999) 17267–17274.
[27] I. Verde, G. Pahlke, M. Salanova, G. Zhang, S. Wang, D. Coletti, J. Onuffer, S.L. Jin, M. Conti, Myomegalin is a novel protein of the golgi/centrosome that interacts with a cyclic nucleotide phosphodiesterase, J. Biol. Chem. 276 (2001) 11189–11198.
[28] A. di Campli, F. Valderrama, T. Babia, M.A. De Matteis, A. Luini, G. Egea, Morphological changes in the Golgi complex correlate with actin cytoskeleton rearrangements, Cell Motil. Cytoskeleton. 43 (1999) 334–348.
[29] F. Valderrama, T. Babia, I. Ayala, J.W. Kok, J. Renau-Piqueras, G. Egea, Actin microfilaments are essential for the cytological positioning and morphology of the Golgi complex, Eur. J. Cell Biol. 76 (1998) 9–17.
[30] J.M. Percival, J.A. Hughes, D.L. Brown, G. Schevzov, K. Heimann, B. Vrhovski, N. Bryce, J.L. Stow, P.W. Gunning, Targeting of a tropomyosin isoform to short microfilaments associated with the Golgi complex, Mol. Biol. Cell 15 (2004) 268–280.
[31] E.A. Holleran, M.K. Tokito, S. Karki, E.L. Holzbaur, Centractin (ARP1) associates with spectrin revealing a potential mechanism to link dynactin to intracellular organelles, J. Cell Biol. 135 (1996) 1815–1829.
[32] K.A. Beck, W.J. Nelson, A spectrin membrane skeleton of the Golgi complex, Biochim. Biophys. Acta 1404 (1998) 153–160.
[33] M.A. De Matteis, J.S. Morrow, The role of ankyrin and spectrin in membrane transport and domain formation, Curr. Opin. Cell Biol. 10 (1998) 542–549.
[34] L.L. Gough, J. Fan, S. Chu, S. Winnick, K.A. Beck, Golgi localization of Syne-1, Mol. Biol. Cell 14 (2003) 2410–2424.
[35] L.L. Gough, K.A. Beck, The spectrin family member Syne-1 functions in retrograde transport from Golgi to ER, Biochim. Biophys. Acta 1693 (2004) 29–36.
[36] A. Godi, I. Santone, P. Pertile, P. Devarajan, P.R. Stabach, J.S. Morrow, G. Di Tullio, R. Polishchuk, T.C. Petrucci, A. Luini, M.A. De Matteis, ADP ribosylation factor regulates spectrin binding to the Golgi complex, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 8607–8612.
[37] A. Siddhanta, A. Radulescu, M.C. Stankewich, J.S. Morrow, D. Shields, Fragmentation of the Golgi apparatus. A role for beta III spectrin and synthesis of phosphatidylinositol 4,5-bisphosphate, J. Biol. Chem. 278 (2003) 1957–1965.
[38] J. Seemann, E. Jokitalo, M. Pypaert, G. Warren, Matrix proteins can generate the higher order architecture of the Golgi apparatus, Nature 407 (2000) 1022–1026.
[39] S.R. Pfeffer, Constructing a Golgi complex, J. Cell Biol. 155 (2001) 873–875.
[40] K.J. Griffith, E.K. Chan, C.C. Lung, J.C. Hamel, X. Guo, K. Miyachi, M.J. Fritzler, Molecular cloning of a novel 97-kd Golgi complex autoantigen associated with Sjogren's syndrome, Arthritis Rheum. 40 (1997) 1693–1702.
[41] Y. Misumi, M. Sohda, A. Yano, T. Fujiwara, Y. Ikehara, Molecular characterization of GCP170, a 170-kDa protein associated with the cytoplasmic face of the Golgi membrane, J. Biol. Chem. 272 (1997) 23851–23858.
[42] M.J. Fritzler, J.C. Hamel, R.L. Ochs, E.K. Chan, Molecular characterization of two human autoantigens: unique cDNAs encoding 95- and 160-kD proteins of a putative family in the Golgi complex, J. Exp. Med. 178 (1993) 49–62.
[43] R. Erlich, P.A. Gleeson, P. Campbell, E. Dietzsch, B.H. Toh, Molecular characterization of *trans*-Golgi p230. A human peripheral membrane protein encoded by a gene on chromosome 6p12-22 contains extensive coiled-coil alphahelical domains and a granin motif, J. Biol. Chem. 271 (1996) 8328–8337.
[44] M.J. Fritzler, C.C. Lung, J.C. Hamel, K.J. Griffith, E.K. Chan, Molecular characterization of Golgin-245, a novel Golgi complex protein containing a granin signature, J. Biol. Chem. 270 (1995) 31262–31268.
[45] A. Jakymiw, E. Raharjo, J.B. Rattner, T. Eystathioy, E.K. Chan, D.J. Fujita, Identification and characterization of a novel Golgi protein, golgin-67, J. Biol. Chem. 275 (2000) 4137–4144.
[46] R.A. Bascom, S. Srinivasan, R.L. Nussbaum, Identification and characterization of golgin-84, a novel Golgi integral membrane protein with a cytoplasmic coiled-coil domain, J. Biol. Chem. 274 (1999) 2953–2962.

[47] B. Short, C. Preisinger, R. Korner, R. Kopajtich, O. Byron, F.A. Barr, A GRASP55-rab2 effector complex linking Golgi structure to membrane traffic, J. Cell Biol. 155 (2001) 877–883.
[48] A.D. Linstedt, H.P. Hauri, Giantin, a novel conserved Golgi membrane protein containing a cytoplasmic domain of at least 350 kDa, Mol. Biol. Cell 4 (1993) 679–693.
[49] A.K. Gillingham, S. Munro, Long coiled-coil proteins and membrane traffic, Biochim. Biophys. Acta 1641 (2003) 71–85.
[50] B.D. Moyer, B.B. Allan, W.E. Balch, Rab1 interaction with a GM130 effector complex regulates COPII vesicle *cis*-Golgi tethering, Traffic 2 (2001) 268–276.
[51] J. Shorter, M.B. Beard, J. Seemann, A.B. Dirac-Svejstrup, G. Warren, Sequential tethering of Golgins and catalysis of SNAREpin assembly by the vesicle-tethering protein p115, J. Cell Biol. 157 (2002) 45–62.
[52] F.A. Barr, M. Puype, J. Vandekerckhove, G. Warren, GRASP65, a protein involved in the stacking of Golgi cisternae, Cell 91 (1997) 253–262.
[53] C.Y. Lin, M.L. Madsen, F.R. Yarm, Y.J. Jang, X. Liu, R.L. Erikson, Peripheral Golgi protein GRASP65 is a target of mitotic polo-like kinase (Plk) and Cdc2, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 12589–12594.
[54] M. Lowe, N.K. Gonatas, G. Warren, The mitotic phosphorylation cycle of the *cis*-Golgi matrix protein GM130, J. Cell Biol. 149 (2000) 341–356.
[55] C. Sutterlin, P. Hsu, A. Mallabiabarrena, V. Malhotra, Fragmentation and dispersal of the pericentriolar Golgi complex is required for entry into mitosis in mammalian cells, Cell 109 (2002) 359–369.
[56] C. Preisinger, R. Korner, M. Wind, W.D. Lehmann, R. Kopajtich, F.A. Barr, Plk1 docking to GRASP65 phosphorylated by Cdk1 suggests a mechanism for Golgi checkpoint signalling, EMBO J. 24 (2005) 753–765.
[57] J. Shorter, R. Watson, M.E. Giannakou, M. Clarke, G. Warren, F.A. Barr, GRASP55, a second mammalian GRASP protein involved in the stacking of Golgi cisternae in a cell-free system, EMBO J. 18 (1999) 4949–4960.
[58] L. Lu, G. Tai, W. Hong, Autoantigen Golgin-97, an effector of Arl1 GTPase, participates in traffic from the endosome to the *trans*-golgi network, Mol. Biol. Cell 15 (2004) 4426–4443.
[59] A. Diao, D. Rahman, D.J. Pappin, J. Lucocq, M. Lowe, The coiled-coil membrane protein golgin-84 is a novel rab effector required for Golgi ribbon formation, J. Cell Biol. 160 (2003) 201–212.
[60] J.C. Reed, K.S. Doctor, A. Godzik, The domains of apoptosis: a genomics perspective, Sci. STKE 2004 (2004) re9.
[61] K.F. Ferri, G. Kroemer, Organelle-specific initiation of cell death pathways, Nat. Cell Biol. 3 (2001) E255–E263.
[62] S.J. Riedl, Y. Shi, Molecular mechanisms of caspase regulation during apoptosis, Nat. Rev., Mol. Cell Biol. 5 (2004) 897–907.
[63] N.A. Thornberry, Y. Lazebnik, Caspases: enemies within, Science 281 (1998) 1312–1316.
[64] Y. Shi, Mechanisms of caspase activation and inhibition during apoptosis, Mol. Cell 9 (2002) 459–470.
[65] K.M. Boatright, G.S. Salvesen, Mechanisms of caspase activation, Curr. Opin. Cell Biol. 15 (2003) 725–731.
[66] J.C. Sharpe, D. Arnoult, R.J. Youle, Control of mitochondrial permeability by Bcl-2 family members, Biochim. Biophys. Acta 1644 (2004) 107–113.
[67] T. Kuwana, D.D. Newmeyer, Bcl-2-family proteins and the role of mitochondria in apoptosis, Curr. Opin. Cell Biol. 15 (2003) 691–699.
[68] N. Morishima, K. Nakanishi, K. Tsuchiya, T. Shibata, E. Seiwa, Translocation of Bim to the endoplasmic reticulum (ER) mediates ER stress signaling for activation of Caspase-12 during ER stress-induced apoptosis, J. Biol. Chem. 279 (2004) 50375–50381.
[69] D.G. Breckenridge, M. Germain, J.P. Mathai, M. Nguyen, G.C. Shore, Regulation of apoptosis by endoplasmic reticulum pathways, Oncogene 22 (2003) 8608–8618.
[70] A.M. Verhagen, E.J. Coulson, D.L. Vaux, Inhibitor of apoptosis proteins and their relatives: IAPs and other BIRPs, Genome Biol. 2 (2001) (REVIEWS3009).
[71] G.S. Salvesen, C.S. Duckett, IAP proteins: blocking the road to death's door, Nat. Rev., Mol. Cell Biol. 3 (2002) 401–410.
[72] S. Hu, X. Yang, Cellular inhibitor of apoptosis 1 and 2 are ubiquitin ligases for the apoptosis inducer Smac/DIABLO, J. Biol. Chem. 278 (2003) 10055–10060.
[73] Y. Huang, Y.C. Park, R.L. Rich, D. Segal, D.G. Myszka, H. Wu, Structural basis of caspase inhibition by XIAP: differential roles of the linker versus the BIR domain, Cell 104 (2001) 781–790.
[74] R.S. Maag, S.W. Hicks, C.E. Machamer, Death from within: apoptosis and the secretory pathway, Curr. Opin. Cell Biol. 15 (2003) 456–461.
[75] M. Mancini, C.E. Machamer, S. Roy, D.W. Nicholson, N.A. Thornberry, L.A. Casciola-Rosen, A. Rosen, Caspase-2 is localized at the Golgi complex and cleaves golgin-160 during apoptosis, J. Cell Biol. 149 (2000) 603–612.
[76] B.C. Baliga, S.H. Read, S. Kumar, The biochemical mechanism of caspase-2 activation, Cell Death Differ. 11 (2004) 1234–1241.
[77] M. Lowe, J.D. Lane, P.G. Woodman, V.J. Allan, Caspase-mediated cleavage of syntaxin 5 and giantin accompanies inhibition of secretory traffic during apoptosis, J. Cell. Sci. 117 (2004) 1139–1150.
[78] H.P. Hauser, M. Bardroff, G. Pyrowolakis, S. Jentsch, A giant ubiquitinconjugating enzyme related to IAP apoptosis inhibitors, J. Cell Biol. 141 (1998) 1415–1422.
[79] S.Y. Vernooy, V. Chow, J. Su, K. Verbrugghe, J. Yang, S. Cole, M.R. Olson, B.A. Hay, *Drosophila* Bruce can potently suppress Rpr- and Grim-dependent but not Hid-dependent cell death, Curr. Biol. 12 (2002) 1164–1168.
[80] T. Bartke, C. Pohl, G. Pyrowolakis, S. Jentsch, Dual role of BRUCE as an antiapoptotic IAP and a chimeric E2/E3 ubiquitin ligase, Mol. Cell 14 (2004) 801–811.
[81] Y. Hao, K. Sekine, A. Kawabata, H. Nakamura, T. Ishioka, H. Ohata, R. Katayama, C. Hashimoto, X. Zhang, T. Noda, T. Tsuruo, M. Naito, Apollon ubiquitinates SMAC and caspase-9, and has an essential cytoprotection function, Nat. Cell Biol. 6 (2004) 849–860.
[82] S.J. Jones, E.C. Ledgerwood, J.B. Prins, J. Galbraith, D.R. Johnson, J.S. Pober, J.R. Bradley, TNF recruits TRADD to the plasma membrane but not the *trans*-Golgi network, the principal subcellular location of TNF-R1, J. Immunol. 162 (1999) 1042–1048.
[83] M. Bennett, K. Macdonald, S.W. Chan, J.P. Luzio, R. Simari, P. Weissberg, Cell surface trafficking of Fas: a rapid mechanism of p53-mediated apoptosis, Science 282 (1998) 290–293.
[84] J.R. Bradley, S. Thiru, J.S. Pober, Disparate localization of 55-kd and 75-kd tumor necrosis factor receptors in human endothelial cells, Am. J. Pathol. 146 (1995) 27–32.
[85] F.G. Gervais, R. Singaraja, S. Xanthoudakis, C.A. Gutekunst, B.R. Leavitt, M. Metzler, A.S. Hackam, J. Tam, J.P. Vaillancourt, V. Houtzager, D.M. Rasper, S. Roy, M.R. Hayden, D.W. Nicholson, Recruitment and activation of caspase-8 by the Huntingtin-interacting protein Hip-1 and a novel partner Hippi, Nat. Cell Biol. 4 (2002) 95–105.
[86] A. Sesso, D.T. Fujiwara, M. Jaeger, R. Jaeger, T.C. Li, M.M. Monteiro, H. Correa, M.A. Ferreira, R.I. Schumacher, J. Belisario, B. Kachar, E.J. Chen, Structural elements common to mitosis and apoptosis, Tissue Cell 31 (1999) 357–371.
[87] J.D. Lane, J. Lucocq, J. Pryde, F.A. Barr, P.G. Woodman, V.J. Allan, M. Lowe, Caspase-mediated cleavage of the stacking protein GRASP65 is required for Golgi fragmentation during apoptosis, J. Cell Biol. 156 (2002) 495–509.
[88] R. Chiu, L. Novikov, S. Mukherjee, D. Shields, A caspase cleavage fragment of p115 induces fragmentation of the Golgi apparatus and apoptosis, J. Cell Biol. 159 (2002) 637–648.
[89] A. Walker, C. Ward, T.A. Sheldrake, I. Dransfield, A.G. Rossi, J.G. Pryde, C. Haslett, Golgi fragmentation during Fas-mediated apoptosis is associated with the rapid loss of GM130, Biochem. Biophys. Res. Commun. 316 (2004) 6–11.

[90] K. Nozawa, C.A. Casiano, J.C. Hamel, C. Molinaro, M.J. Fritzler, E.K. Chan, Fragmentation of Golgi complex and Golgi autoantigens during apoptosis and necrosis, Arthritis Res. 4 (2002) R3.
[91] J.D. Lane, M.A. Vergnolle, P.G. Woodman, V.J. Allan, Apoptotic cleavage of cytoplasmic dynein intermediate chain and p150(Glued) stops dynein-dependent membrane motility, J. Cell Biol. 153 (2001) 1415–1426.
[92] R.S. Maag, M. Mancini, A. Rosen, C.E. Machamer, Caspase-resistant golgin- 160 disrupts apoptosis induced by secretory pathway stress and ligation of death receptors, Mol. Biol. Cell (2005) (in press).
[93] S.W. Hicks, C.E. Machamer, The NH2-terminal domain of Golgin-160 contains both Golgi and nuclear targeting information, J. Biol. Chem. 277 (2002) 35833–35839.
[94] D.T. Rutkowski, R.J. Kaufman, A trip to the ER: coping with stress, Trends Cell Biol. 14 (2004) 20–28.
[95] J. Ramos-Castaneda, Y.N. Park, M. Liu, K. Hauser, H. Rudolph, G.E. Shull, M.F. Jonkman, K. Mori, S. Ikeda, H. Ogawa, P. Arvan, Deficiency of ATP2C1, a golgi ion pump, induces secretory pathway defects in ER-associated degradation and sensitivity to ER-stress, J. Biol. Chem. 280 (2004) 9467–9473.
[96] P. Arvan, X. Zhao, J. Ramos-Castaneda, A. Chang, Secretory pathway quality control operating in Golgi, plasmalemmal, and endosomal systems, Traffic 3 (2002) 771–780.
[97] S. Mogelsvang, B.J. Marsh, M.S. Ladinsky, K.E. Howell, Predicting function from structure: 3D structure studies of the mammalian Golgi complex, Traffic 5 (2004) 338–345.
[98] K. Hanada, K. Kumagai, S. Yasuda, Y. Miura, M. Kawano, M. Fukasawa, M. Nishijima, Molecular machinery for non-vesicular trafficking of ceramide, Nature 426 (2003) 803–809.
[99] W.J. van Blitterswijk, A.H. van der Luit, R.J. Veldman, M. Verheij, J. Borst, Ceramide: second messenger or modulator of membrane structure and dynamics? Biochem. J. 369 (2003) 199–211.
[100] E.M. Bevers, P. Comfurius, D.W. Dekkers, R.F. Zwaal, Lipid translocation across the plasma membrane of mammalian cells, Biochim. Biophys. Acta 1439 (1999) 317–330.
[101] M.R. Rippo, F. Malisan, L. Ravagnan, B. Tomassini, I. Condo, P. Costantini, S.A. Susin, A. Rufini, M. Todaro, G. Kroemer, R. Testi, GD3 ganglioside directly targets mitochondria in a bcl-2-controlled fashion, FASEB J. 14 (2000) 2047–2054.
[102] C. Garcia-Ruiz, A. Colell, A. Morales, M. Calvo, C. Enrich, J.C. Fernandez-Checa, Trafficking of ganglioside GD3 to mitochondria by tumor necrosis factoralpha, J. Biol. Chem. 277 (2002) 36443–36448.
[103] B. Tomassini, F. Malisan, L. Franchi, C. Nicolo, G.B. Calvo, T. Saito, R. Testi, Calnexin suppresses GD3 synthase-induced apoptosis, FASEB J. 18 (2004) 1553–1555.
[104] M. Sorice, A. Circella, I.M. Cristea, T. Garofalo, L. Di Renzo, C. Alessandri, G. Valesini, M.D. Esposti, Cardiolipin and its metabolites move from mitochondria to other cellular membranes during death receptor-mediated apoptosis, Cell Death Differ. 11 (2004) 1133–1145.
[105] I.M. Cristea, M. Degli Esposti, Membrane lipids and cell death: an overview, Chem. Phys. Lipids 129 (2004) 133–160.